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10/059,920	01/29/2002	Michael A. Adams	PTQ-0040	4865

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EXAMINER	
NICKOL, GARY B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-89* is/are pending in the application.

4a) Of the above claim(s) *51-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

4) ☐ Interview Summary (PTO-413)

Adams *et al.*

Date of priority: May 1, 1998

Claims 51-89 are pending.

Claims 51-80 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 81-89 are currently under consideration.

The Election filed February 25, 2004 in response to the Office Action of January 26, 2004 is acknowledged and has been entered.

Applicant's election with traverse of Group XIV, claims 81-89 is acknowledged. The traversal is on the ground(s) that an examination of all groups (including those in the same classification) would not impose a serious burden on the examiner. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the Action mailed 01/26/04. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, i.e. a "Method for Diagnosing a Vascular Condition" does not appear to be indicative of assessing risk of metastasis.

Claim Objections

Claims 81-89 are objected to because they include subject matter drawn to a non-elected invention. The objection can be obviated by amending claim 81, 87 wherein "PAI-1" is omitted. Applicants should further amend the claimed subject matter to grammatically reflect measuring two genes instead of "at least two of.." since only two genes are measured.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-84 are rejected as vague and indefinite. It is unclear how the reference sample can be used as a standard for ascertaining risk of metastasis when the reference sample is also derived from the same individual. For example, if both the biological sample and the reference sample are derived from the blood or serum of the same individual, would there be a discernable difference in the amount of each gene?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method of assessing risk of metastasis in an individual comprising measuring RTP/Drg1 and uPAR gene product levels in a biological sample; comparing the measured gene product levels in the biological sample to corresponding gene product levels in a reference sample, wherein an increase in one or more of said gene product levels in the biological sample as compared to the levels in the reference sample is indicative of increased risk of metastasis in the individual. The claims further include wherein two or more gene product levels are increased (Claim 82) and further includes the steps of isolating cells from the individual and measuring the invasiveness of said cells in an in vitro cellular assay.

However, the claims are not enabled because one of skill in the art would not be able to predictably assess the risk of metastasis by simply carrying out the steps of the claimed method.

In particular, the steps of assessing the risk of metastasis require two outcomes: (1) that at least *one* of the gene product levels in the biological sample be increased compared to the levels in a reference sample or (2) that both gene product levels are increased.

Thus, one reasonable interpretation of the claims, is a method of assessing the risk of metastasis by observing increased levels of RTP/Drg1 gene levels compared to a reference sample or by observing increased levels of both RTP/Drg1 and uPAR gene product levels compared to their respective reference samples.

However, the specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to assess the risk of metastasis by measuring increased amounts of RTP/Drg1 compared to a reference sample. The specification is devoid of any comparison (either *in vitro* or *in vivo*) of assessing metastasis by observing increased levels of RTP/Drg1 gene product levels. Further, the state of the art and the nature of the invention suggests the opposite; that RTP/Drg1 gene levels would *decrease* compared to a reference sample. Van Belzen *et al.* (Lab.Invest., 1997, Vol. 77, No. 1, pp 85-92, IDS) compared Drg1 expression levels in neoplastic colon tissue versus normal colon tissue. In matched biopsies taken from normal colon mucosa and adenomas from three patients, Drg1 mRNA levels in the adenomas were 2.4-, 4.5- and 7.6-fold lower, respectively, compared to normal tissue. In addition, Drg1 mRNA levels in five surgically removed adenocarcinomas were found to be decreased 2.5- to 12.6-fold compared to the mean expression level in the normal tissue (pages 86-87). Additionally, in agreement with the RNA expression data, Drg1 protein levels appeared higher in differentiated HT29-D4 and Caco-2 cells than in undifferentiated cells, and higher in normal versus neoplastic colon tissue (page 87, 2nd column). Overall, the authors suggest that

Drg1 is up-regulated during differentiation of colon epithelium cells *in vitro* and *in vivo*, and down-regulated in colorectal neoplasms.

Thus, based on the lack of guidance and evidence in the specification and due to the teachings in the prior art, it would appear that one of ordinary skill in the art would not have a reasonable expectation of success in assessing the risk of metastasis by observing an increased amount of RTP/Drg1 compared to a reference sample. Thus, it would require undue experimentation to practice the invention as claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

April 26, 2004

Gary B Nickol

GARY NICKOL
PRIMARY EXAMINER